water molecules and water molecules containing "free" OH groups and "free" lone pairs. However, this theory cannot easily be applied to the anion induced process reported here.
(15) Kinetic salt effects have been earlier ascribed to water polarization as a result of specific interactions with cations or anions: (a) A. R. Olson and L. K. J. Tong, *J. Am. Chem. Soc.*, **66**, 1555 (1944); (b) D. B. Dennison, G. A. Gettys, D. G. Kubler, and D. Shepard, *J. Org. Chem.*, **41**, 2344 (1976).
(16) L. Menninga, Ph.D. Thesis, Groningen, 1976.

Regiospecific α-Tropolone Synthesis. A Selective Preparation of the Isomeric Thujaplicins

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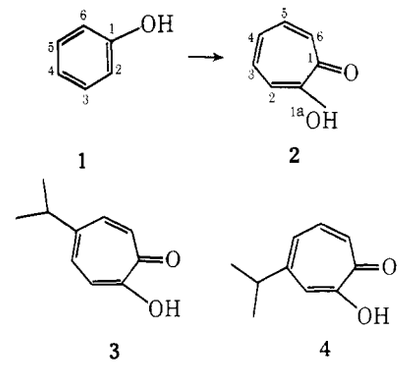
The seven-membered, aromatic α-tropolone ring **2** occurs naturally in three biosynthetically distinct classes:[1,2] in the essential oils of *Cupressae* (e.g., α-thujaplicin), in mold metabolites of the *Penicillium* family (e.g., stipitatonic acid) and in the *Colchicum* alkaloids (e.g., colchicine). The unique character of these seven-membered carbocycles has attracted considerable synthetic, biogenetic, and theoretical attention[3] since the structure elucidation of the first natural α-tropolone, stipitatonic acid by Dewar, in 1945. However, general synthetic entry into the α-tropolone system has been limited for the most part to the exhaustive oxidation of α-ketocycloheptanones[3] or the $[_\pi 2_s + _\pi 2_a]$ cycloaddition of dihaloketenes with cyclopentadienes followed by rearrangement.[3,4]

As a general approach to natural α-tropolone systems, we desired synthetic access to the α-tropolone ring via site-specific single-carbon expansion of the corresponding suitably substituted phenol (e.g., 1 → 2). This approach allows the utilization of well-defined phenolic chemistry in establishing the requisite substitution pattern or functionality on the ultimately generated α-tropolone ring and minimizes subsequent chemical manipulation in the presence of the α-tropolone system. We wish to report the realization of this general synthetic objective as illustrated by regiospecific syntheses of the isomeric thujaplicins γ-3 and β-4.



Our synthetic scheme called for the regiospecific establishment of a dihydroaromatic silyl ether. The recent development of lithium/ammonia reduction of O-silylated phenols affords excellent regiopredictability and facile synthetic entry into such systems.[7] For the synthesis of γ-thujaplicin **3** (Scheme I), dissolving metal reduction of triethylsilyl (4-isopropylphenyl) ether **5** afforded the dihydroaromatic silyl ether **6**. Subsequent sodium trichloroacetate mediated dichlorocyclopropanation and methanolic aqueous hydrochloric acid hydrolysis[9,10] afforded the stable bicyclic dichlorocyclopropanol **7**. The regiospecificity of dichlorocyclopropanation is well established to proceed via attack on the most nucleophilic olefin in cases not overshadowed by steric considerations. The stability of such unsaturated bicyclic α,α-dichlorocyclopropanols appears to be unique and **7** is thus a representative of a novel class of functionalized cyclopropane.[11,12] *syn*-Hydroxyl directed peracid epoxidation afforded the epoxide **8** which

Table I. Physical Data for Isolated Intermediates in γ-Thujaplicin Synthesis

	registry no.	bp, °C/mm or Mp, °C	IR, cm^{-1}	NMR ($CDCl_3/Me_4Si$), δ	MS (*m/e*) rel abundance, %
5	66967-06-4	155–165/0.1	1580 (w) 1250 (s) 740 (s)	0.48–1.05 (brm, 15 H) 1.13 (d, *J* = 6.5 Hz, 6 H) 2.75 (q, *J* = 6.5 Hz, 1 H) 7.75 (d, *J* = 10 Hz, 2 H) 8.05 (d, *J* = 10 Hz, 2 H)	250 (81) 235 (73) 195 (95) 121 (100)
6	66967-07-5	Kugelrohr 150/0.1	1610 (med) 1250 (stg)	1.05–0.50 (m, 21 H) 2.30 (b, qt, *J* = 7.0 Hz, 1 H) 2.65 (s, 2 H) 4.85 (s, 1 H) 5.35 (s, 2 H)	
7[a]	66967-08-6	white spindles 71.0–73.5	3425 (stg) 850 (stg)	0.97 (d, *J* = 7.0 Hz, 6 H) 1.82 (d, d, *J* = 7.5, 1.5 Hz, 1 H) 1.90–2.50 (m, 3 H) 2.64 (d, d, *J* = 6.5, 4.5 Hz, 2 H) 2.95 (brs, **OH**, 1 H) 5.30 (brs, 1 H)	220 (16) 185 (89) 167 (33) 97 (100
8[a,17]	66967-09-7	white blocks 75–77	3420 (stg) 1040 (stg) 830 (stg)	0.94 (d, d, *J* = 6.5 Hz, 6 H) 1.50 (qt, *J* = 6.5 Hz, 1 H) 1.62 (d, d, *J* = 9.0, 2.0 Hz, 1 H) 1.83 (d, d, *J* = 16.0, 2.0 Hz, 1 H) 2.31 (d, d, *J* = 16.0, 9.0 Hz, 1 H) 2.5 (d, *J* = 2.0 Hz, 2 H) 2.79 (t, *J* = 2.0 Hz, 1 H)	236 (4.2) 201 (65) 193 (96) 175 (88) 157 (100)
9[a]	66967-10-0	light oil	1622 (stg) 1599 (stg) 940 (stg)	1.20 (d, *J* = 8.0 Hz, 6 H) 2.80 (qt, *J* = 8.0 Hz, 1 H) 6.74 (d, *J* = 10.5 Hz, 1 H) 7.12 (s, 2 H) 7.65 (d, *J* = 10.5 Hz, 1 H)	182 (79) 139 (100) 109 (32) 103 (59)

[a] Satisfactory elemental analysis was obtained (C, H ±0.3%).

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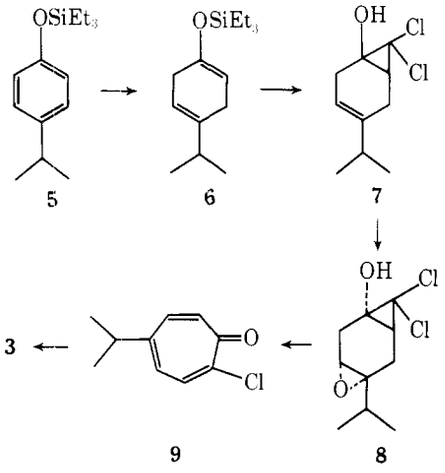
Table II. Physical Data for Isolated Intemediates in δ-Thujaplicin Synthesis

	registry no.	bp, °C/mm	IR, cm^{-1}	NMR ($CDCl_3/Me_4Si$), δ	MS (*m/e*) rel abundance, %
10	66967-11-1	150–162/0.1	1580 (w med) 1260 (stg) 750 (stg)	0.60–1.10 (m, 15 H) 0.60–1.10 (d, J = 7.0 Hz, 6 H) 2.82 (q, J = 7.0 Hz, 1 H) 6.50–6.82 (m, 3 H) 7.08 (t, J = 9.0 Hz, 1 H)	
11	66967-12-2	Kugelrohr 150°/0.1 mm	1650 (med) 1250 (stg) 730 (stg)	1.16–1.78 (m, 21 H) 2.92 (t, J = 7.0 Hz, 1 H) 5.48 (br, s, 1 H) 6.00 (br, s, 1 H)	
12[a]	66967-13-3	154/0.1 colorless oil	3350 (stg) 1020 (stg)	0.97 (d, J = 7.0 Hz, 6 H) 1.80 (d, d, J = 7.5, 1.5 Hz, 1 H) 1.96–2.40 (m, 3 H) 2.50–2.70 (m, 2 H) 3.20 (b, s, **OH**, 1 H) 5.20 (s, 1 H)	220 (25) 185 (96) 167 (35) 97 (100)
13	66967-14-4	colorless oil	3325 (brd, stg) 1280 (stg) 770 (stg)	0.93 (br, t, J = 8.0 Hz, 6 H) 1.45 (q, J = 8.0 Hz, 1 H) 1.55 (br, d, J = 9.0 Hz, 1 H) 1.85 (d, t, J = 16.0, 2.5 Hz, 1 H) 2.24 (d, J = 15.5 Hz, 1 H) 2.45 (d, J = 15.5 Hz, 1 H) 2.50 (d, d, d, J = 2.0, 9.5, 16.0 Hz, 1 H) 2.83 (br, s, 1 H) 3.50 (br, s, **OH**, 1 H)	236 (5.5) 201 (58) 193 (100) 175 (85) 157 (100)
14[a]	66967-15-5	light oil	1595 (stg) 1630 (stg) 900 (stg)	1.18 (d, J = 8.0 Hz 6 H) 2.72 (q, J = 8.0 Hz, 1 H) 6.50–6.80 (m, 2 H) 6.96 (d, d, J = 8.5, 1.10 Hz, 1 H) 7.48 (d, d, J = 6.0, 9.5 Hz, 1 H)	182 (59) 139 (100) 109 (45) 103 (65)

[a] Satisfactory elemental analysis was obtained (C, H ±0.3%).

Scheme I

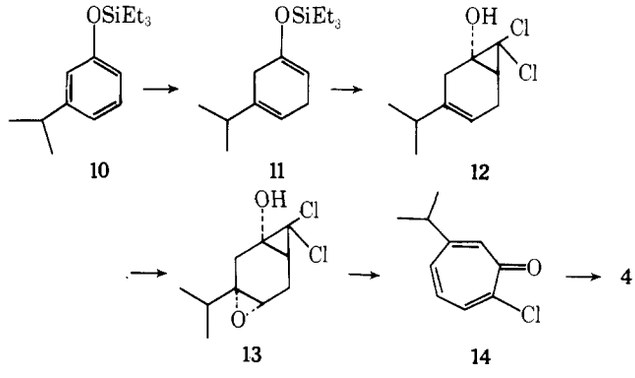


upon treatment in refluxing benzene with a trace of *p*-toluenesulfonic acid catalyst gave the α-chlorotropone **9**. Conversion of the α-chlorotopone **9** to γ-thujaplicin **3** by treatment with aqueous phosphoric acid in acetic acid at reflux[13] completed the synthesis.

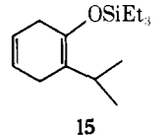
In a similar fashion, triethylsilyl 3-isopropylphenyl ether **10** (Scheme II) could be reduced to dienylsilyl ether **11** then dichlorocyclopropanated and hydrolyzed to give the dichlorononorcarenol **12**. Subsequent conversion of norcarenol **12** to epoxide **13** and acid-catalyzed ring expansion afforded the α-chlorotropone **14**. Again completion of the synthesis could be effected by strong acid treatment of α-chlorotropone **14** to generate β-thujaplicin **4**. Proceeding along identical lines, phenol **1** could be converted into α-tropolone **2**.

This phenol to α-tropolone conversion is direct in its synthetic manipulation, efficient in its yield, and reasonably general in synthetic applicability. The principle difficulty

Scheme II



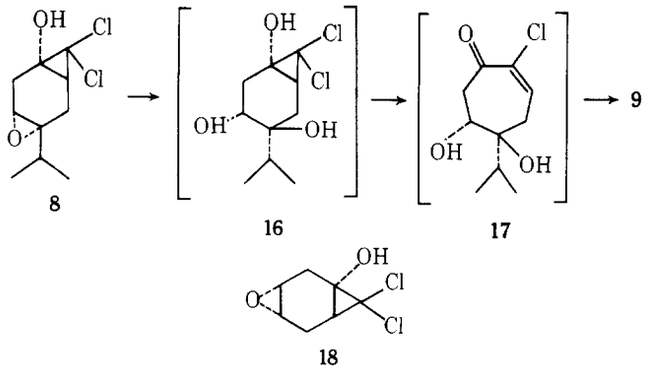
encountered in the scheme is the effective and regiospecific dichlorocyclopropanation of hindered enol silyl ethers. Although enhanced nucleoplilicity of the enol silyl ether unsaturation ensures highly regioselective (>95%) olefin reactivity in the α-tropolone and β- and γ-thujaplicin syntheses, the dichlorocyclopropanation of cyclohexadienyl silyl ether **15**, an intermediate in proposed α-thujaplicin preparation, proceeded in unserviceably low yield (~12%). Apparently, steric hindrance to olefin access inhibits enol silyl ether reactivity.



15

The high yield rearrangement of the norcaranol oxide system (**8** and **13**) directly to the α-chlorotropone (**9** and **14**) represents an interesting synthetic transformation. The process is acid catalyzed and corresponds to an overall ring

Scheme III



expansion–bisdehydration of the resultant α-chloroenone system. In the γ-thujaplicin sequence, both the epoxide 8 (refluxing toluene, $t_{1/2} \gg 24$ h) and the parent olefin 7 (refluxing toluene or *n*-butyl alcohol–water, $t_{1/2} \gg 24$ h) possess excellent thermal stability. In addition, the parent norcarenol 7 is stable to the acidic conditions required for epoxide 8 rearrangement. Thus, the suggested mechanism for this ring expanding transformation (e.g., 8 → 9) is acid catalyzed *epoxide opening* to generate the bicyclic triol **16**, followed by facile ring enlargement to the α-chloroenone diol **17** (Scheme III). Subsequent acid mediated bisdehydration produces the α-chlorotropone **9**. The rate-determing step must be epoxide opening, since no intermediates chould be detected (TLC) in the conversion of 8 to 9.

This postulated rate-determining oxirane opening requires rapid (or spontaneous) ring expansion of the saturated 7,7-dichloronorcaran-1-ol structure **16** (to **17**), which is generated upon release of the C-3–C-4 constraint on the norcaranol system. The rapid rearrangement of saturated 7,7-dichloronorcaranol systems relative to their $\Delta^{3,4}$-unsaturated counterparts has been observed.[11] Furthermore, the observation that trisubstituted norcaranol oxide 8 rearranges at a rate faster than the corresponding disubstituted norcaranol oxide 18 (competitively in the same reaction media) is consistent with rate-determining electrophilic epoxide opening. Such an oxirane substitution–reactivity pattern is a consequence of enhanced stability of the transition state incipient carbocation for the alkyl substituted oxirane 8 relative to the unsubstituted analogue 18.

In addition, the regiospecific conversion of the α-chlorotropone structures generated via this route to specific 2-substituted troponoids has considerable synthetic potential. For example, regiospecific displacement of the α-chloro substituent by methoxide under known conditions would generate specific *O*-methyltropolones.[14] Alternate schemes for tropolone *O*-methylation proceeding via the parent α-tropolone generally yield *O*-methyltropolone isomers as a consequence of facile α-tropolone tautomerization. Thus, diazomethane methylation of *O*-demethylcolchicine affords both colchicine and isocolchicine.[15] In principle, regiospecific α-chlorotropone generation and subsequent nucleophilic introduction of methoxide could circumvent such isomer formation.

Experimental Section

General. Melting points were taken with a Thomas-Hoover apparatus using open capillaries and are uncorrected. Proton magnetic resonance spectra were recorded at 100 MHz with a Jeol JNM-MH-100 spectrometer employing tetramethylsilane as an internal standard. Low resolution mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV. The parent ion and the most intense peaks (2–4) are reported. Infrared spectra were obtained on a Perkin-Elmer 727 infrared spectrometer. Elemental analyses were preformed by Galbraith Laboratories, Inc., Knoxville, Tenn. For all column chromatography, E. Merck (type 60) silica gel and short column techniques were utilized and for TLC analysis, E. Merck Silica Gel 60, F-254 precoated (0.25 mm) plates were employed. Magnesium sulfate was used as the drying agent throughout and all experimental procedures were performed under an atmosphere of dry nitrogen.

Physical data for the intermediate compounds described in the experimental procedures are presented in Table I (γ-thujaplicin synthesis) and Table II (β-thujaplicin synthesis).

General Triethylsilyl Phenyl Ether Synthesis.[8] The requisite phenol (50.0 mmol) was dissolved in anhydrous dimethyl formamide (40 mL) to which imidazole (8.50 g, 125.0 mmol) and triethylchlorosilane (9.00 g, 0.06 mmol) were subsequently added. The solution was heated at reflux, maintained for 3 h, allowed to cool (~1 h), then poured into pentane (150 mL) and extracted with cold 1 N aqueous sodium bicarbonate, water, and brine. The organic layer was dried and the solvent removed in vacuo affording the triethylsilyl phenyl ether (48.0 mmol, 96%) sufficiently pure (~95%, VPC) to employ in the reduction step without purification. If the triethylsilyl phenyl ether is to be stored for extended periods (~4 months) distillation is suggested. In addition, phenols reluctant to undergo *O*-silylation (e.g., 2-isopropylphenol) require extended periods at reflux (~12 h) and distillation prior to use.

Isopropyl-7,7-dichloronorcar-3-en-1-ols 10 and 15. (a) Dissolving Metal Reduction of Triethylsilyl Isopropylphenyl Ethers. The method of Donaldson and Fuchs[8] can be employed without modification. However, our initial studies utilized an alternate procedure which might prove useful in larger scale (>20 mmol) phenyl silyl ether reduction and which produces comparable yields when undertaken with triethylsilyl phenyl ethers. This modified procedure is described here.

Isopropylphenyl triethylsilyl ether **5** or **10** (2.50 g, 10.0 mmol) was introduced (in 10 mL of anhydrous THF) via syringe to a −33 °C solution of anhydrous THF (55 mL), *tert*-butyl alcohol (10 mL), and ammonia (120 mL) containing lithium wire (70.0 mmol), The reaction mixture was maintained at reflux for 35 min, then cooled to −78 °C, quenched with ammonium chloride (4.0 g), and then hexane (150 mL) was introduced carefully. With rapid stirring and gentle warming the bulk of the ammonia is allowed to evaporate over the course of ¾ h. Subsequent partitioning of the mixture between hexane (150 mL) and saturated ammonium chloride solution (200 mL) followed by drying the organic layer and solvent removal afforded the crude dihydroaromatic enol ethers **6** (2.226 g, ~90% reduced) and **11** (2.090 g, ~90% reduced). The sole impurity was unreduced (and noninterfering) starting material and the crude product was consequently utilized without further purification.

(b) Dihydroaromatic Triethylsilyl Enol Ether Cyclopropanation. The crude dihydroaromatic silyl ether **6** or **11** (~9.0 mmol) was dissolved in freshly distilled tetrachloroethylene (10 mL) and anhydrous dimethoxyethane (10 mL), to which anhydrous sodium trichloroacetate (2.100 g, 11.25 mmol) was introduced, and the suspension was refluxed for 1.5 h. The solution was then cooled, poured into pentane (150 mL), and washed rapidly with water then brine and the organic layer was dried. Solvent removal in vacuo afforded the crude silyloxy norcarene compounds which were immediately subjected to silyl ether hydrolysis.

(c) Methanolic Aqueous Hydrochloric Acid Hydrolysis. The crude product silyloxy norcarene was dissolved in a solution of methanol (150 mL) and 10% (by volume) aqueous hydrochloric acid (50 mL) then stirred at room temperature overnight. The mixture was partitioned between ether (300 mL) and water (200 mL); the ethereal layer was washed once with water then brine and dried. Chromatography (4% ethyl acetate/pentane) afforded dichloronorcarenols **7** (1.433 g, 65% based on starting ether **5**) and **12** (1.270 g, 58%).

7,7-Dichloronorcaron-1-ol Oxides 8 and 13. The precursor norcarenol **7** (or **12**) (0.880 g, 4.00 mmol) was dissolved in anhydrous methylene chloride (75 mL) and *m*-chloroperbenzoic acid (1.550 g, 7.6 mmol) was added and the mixture stirred at room temperature. After 2 h, excess peracid was destroyed by stirring with aqueous thiosulfate solution. The resultant solution was partitioned between ether and water and the ethereal layer was washed once with water then brine and subsequently dried. Solvent removal in vacuo followed by chromatography (10% ethyl acetate/pentane) afforded the epoxides **8** (0.861 g, 91%), **17**, and **13** (0.897 g, 95%).

2-Chloro-5(or 6)-isopropyltropone 12 (or 17). The precursor norcarane oxide **11** (or **16**) (0.306 g, 1.29 mmol) was dissolved in benzene (70 mL) containing *p*-toluenesulfonic acid (~25 mg) and refluxed for 2.5 h. The reaction mixture was then cooled and partioned between ether and 3% aqueous sodium bicarbonate. The ethereal layer was washed with brine and dried and the solvent removed in vacuo affording the crude α-chlorotropone. Chromatography (12% ethyl acetate/pentane) gave the isomeric isopropylchlorotropones as col-

orless oils **12** (0.213 g, 91%) and **17** (0.195 g, 78%).

Thujaplicin. The requisite α-chlorotropone **9** or **14** (0.207 g, 1.11 mmol) was dissolved in glatial acetic acid (10 mL) containing aqueous phosphoric acid (44%; 8 ml) and heated at reflux for 15 h.[13] The reaction mixture was then cooled and poured into water (40 mL) and the solution pH adjusted to pH 4–5 with aqueous sodium hydroxide. The aqueous phase was extracted with methylene chloride (5 × 20 mL) then the combined organics dried and the solvent removed in vacuo. Chromatographic filtration (Silica Gel; ether (50%)/pentane) afforded γ-thujaplicin (**3**) [mp 75–77 °C (lit.[16] mp 82 °C)] (0.142 g, 78%) and β-thujaplicin (**4**) [mp 44–46 °C (lit.[16] mp 50–52 °C)] (0.150 g, 83%).

Acknowledgment. The author is grateful for the financial assistance of the Vanderbilt University Natural Science Committee.

Registry No.—16, 66967-16-6; 17' 66967-17-7; 4-isopropylphenol, 99-89-8; 3-isopropylphenol, 618-45-1; triethylchlorosilane, 994-30-9.

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(2) The α-tropolone ring system occurs naturally incorporated in the fused aromatic systems of benzotropolones[2a] and tropoloisoquinolines.[2b] (a) D. Ollis, D. T. Coxon, A. Holmes, and V. C. Vora, *Tetrahedron Lett.*, 5237 (1970); (b) J. V. Silverton, C. Kabuto, K. T. Buck, and M. P. Cava, *J. Am. Chem. Soc.*, **99**, 6708 (1977).
(3) For a review covering troponoid synthesis and chemistry see: F. Pietra, *Chem. Rev.*, **73**, 293 (1973).
(4) For an alternate synthesis of the isomeric thujaplicins proceeding from the corresponding tropone see: R. Noyori, S. Makino, T. Okita, and Y. Hayakawa, *J. Org. Chem.*, **40**, 807 (1976).
(5) Such a "six to seven membered ring expanding" approach to troponoids and tropolonoids has appealed to synthetic chemists for some time. Birch and Keeton[5a,b] and Doering and Detert[6b] employed six to seven ring expansion in their syntheses of the tropone ring system and Tobinaga et al.[6a] utilized a less generalized homologation scheme in their synthesis of the α-tropolone ring in colchicine. (a) A. J. Birch and R. Keeton, *J. Chem. Soc. C*, 109 (1968); (b) A. J. Birch and R. Keeton, *Aust. J. Chem.*, **24**, 331 (1971).
(6) (a) S. Tobinaga, E. Kootani, and F. Miyazaki, *J. Chem. Soc., Chem. Commun.*, 300 (1974); (b) W. V. E. Doering and F. L. Detert, *J. Am. Chem. Soc.*, **73**, 876 (1951).
(7) The work of Donaldson and Fuchs[8] was published concurrent with our own investigation in this area. Only minor differences need be noted. To retain continuity with our earlier work on the dichlorocyclopropanation of trialkylsilyl enol ethers,[9] our studies employed triethylsilyl phenyl ethers, instead of *tert*-butyldimethylsilyl phenyl ethers. As noted by Donaldson and Fuchs,[8] trimethylsilyl phenyl ethers are too labile under the dissolving metal conditions to be useful. However, triethylsilyl phenyl ethers are at least as stable as the corresponding *tert*-butyldimethylsilyl phenyl ethers to the reaction conditions.
(8) R. E. Donaldson and P. L. Fuchs, *J. Org. Chem.*, **52**, 2032 (1977).
(9) G. Stork and T. L. Macdonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975).
(10) J. M. Conia, P. Amico, and C. Blanco, *Synthesis*, 196 (1976).
(11) T. L. Macdonald, *J. Org. Chem.*, in press.
(12) Birch and Keeton[5b] have isolated two related dichlorocyclopropanols. To the best of our knowledge, these compounds represent the only previously isolated α,α-dichlorocyclopropanols.
(13) For example, see: T. Nozoe, T. Asao, E. Takahasi, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **39**, 1310 (1966).
(14) (a) M. Cavazza, R. Cabrino, and F. Pietra, *Synthesis*, 298 (1977); (b) R. Cabrino, M. Cavazza, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 721 (1976).
(15) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **40**, 193 (1957).
(16) T. Nozoe, *Fortschr. Chem. Org. Naturst.*, **13**, 232 (1956).
(17) ^{13}C NMR data were obtained for this compound. The author would like to acknowledge the assistance of Kevin Darst. Chemical shifts (in ppm downfield from Me_4Si) 17.74, 18.42, 18.65, 28.44, 31.70, 34.92, 58.55, 58.83, 61.85, 68.30.

Synthesis of (3*S*,4*S*)-4-Amino-3-hydroxy-6-methylheptanoic Acid Derivatives. Analysis of Diastereomeric Purity

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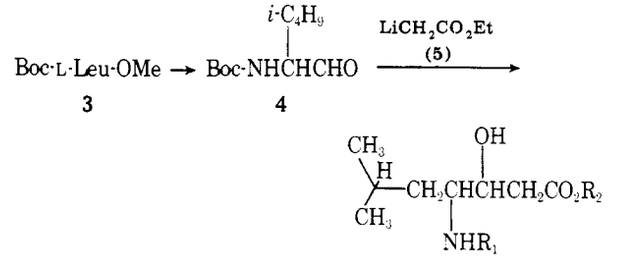
Pepstatin, isovaleryl-L-valyl-L-valyl-(3*S*,4*S*)-statyl-L-alanyl-(3*S*,4*S*)-statine (**1**),[1] is a low molecular weight inhibitor of acid proteases, e.g., pepsin, renin, and cathepsin D.[2] Pepstatin contains the novel amino acid statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (**2a**). Kinetic studies have shown that the (3*S*)-hydroxyl group in the statine residue in position 3 of pepstatin is necessary for tight-binding-inhibition of pepsin.[3,4] Synthetic statine is needed to further study the kinetic and biological properties of pepstatin and the importance of the (3*S*)-hydroxyl group of statine requires that its stereochemistry be rigorously established. However, while several syntheses of statine **2** have been reported,[5-8] the preparation of (3*S*,4*S*)-statine free of contamination from the (3*R*,4*S*) diastereomer is not readily achieved. We report here a convenient, high-yield synthesis of (3*S*,4*S*)-statine via a route that allows for separation of diastereomers and for determination of optical purity.

Scheme I



2a, $R_1 = R_2 = H$ (3*S*,4*S*)
b, $R_1 = R_2 = H$ (3*R*,4*S*)
5a, $R_1 = Boc$; $R_2 = C_2H_5$ (3*S*,4*S*)
b, $R_1 = Boc$; $R_2 = C_2H_5$ (3*R*,4*S*)
6a, $R_1 = Boc$; $R_2 = H$ (3*S*,4*S*)
b, $R_1 = Boc$; $R_2 = H$ (3*R*,4*S*)

Results and Discussion

The preparation of statine derivatives is outlined in Scheme I. Boc-L-leucine methyl ester (**3**) was reduced with diisobutylaluminum hydride in toluene at −78 °C for 6 min. Excess hydride was destroyed with methanol,[9] and the reaction worked up using Rochelle salt[10] to solubilize the complex. Aldehyde **4** was isolated in 85% yield. Addition of lithium ethyl acetate (**5**) at −78 °C to **4** according to a modification of the procedure of Steulmann and Klostermeyer[7] gave an 80% yield of the ester **5a,b** as a mixture of diastereomers (60% (3*S*,4*S*); 40% (3*R*,4*S*)). Diastereomers **5a** and **5b** can be separated by standard column chromatography over silica gel. A better and faster separation is achieved by using commercially prepared columns (Lobar) (3.7 × 44 cm) which can provide 1–2 g of pure **5a** from 2–4 g of the mixture in only a few hours. The overall yield of pure Boc-(3*S*,4*S*)-statine ethyl ester **5a** from ester **3** is 38–40%. Saponification of ester **5a** gives acid **6a** (86%) which, in turn, is readily converted to free statine **2a** by mild acid hydrolysis with trifluoroacetic acid.

Both Boc acids **6a** and **6b** can be crystallized from diethyl ether–petroleum ether (30–60 °C) mixtures. It was possible to isolate the less soluble **6b** by fractional crystallization of the mixture of diastereomers but further concentration of the mother liquor gave **6a** in only 80% optical purity. We were unable to crystallize either **6a** or **6b** from isopropyl alcohol.[7]

A convenient method for establishing the optical purity of the various statine diastereomers has been needed. Diastereomers **2a** and **2b** do not easily separate when subjected to standard amino acid analysis and other ion exchange conditions[8] although separation can be achieved at high temperatures.[6] We have found that the esters **5a** and **5b** are easily separated by gas-liquid chromatography (GC) on an OV-225 column. A mass spectrum of the material eluting from the GC column shows that the diastereomers are chromatographing as the intact Boc esters **5a** and **5b** and have not been degraded

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